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Primer

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Cardiac tamponade

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Abstract

Cardiac tamponade is a medical emergency caused by the progressive accumulation of pericardial fluid (effusion), blood, pus or air in the pericardium, compressing the heart chambers and leading to haemodynamic compromise, circulatory shock, cardiac arrest and death. Pericardial diseases of any aetiology as well as complications of interventional and surgical procedures or chest trauma can cause cardiac tamponade. Tamponade can be precipitated in patients with pericardial effusion by dehydration or exposure to certain medications, particularly vasodilators or intravenous diuretics. Key clinical findings in patients with cardiac tamponade are hypotension, increased jugular venous pressure and distant heart sounds (Beck triad). Dyspnoea can progress to orthopnoea (with no rales on lung auscultation) accompanied by weakness, fatigue, tachycardia and oliguria. In tamponade caused by acute pericarditis, the patient can experience fever and typical chest pain increasing on inspiration and radiating to the trapezius ridge. Generally, cardiac tamponade is a clinical diagnosis that can be confirmed using various imaging modalities, principally echocardiography. Cardiac tamponade is preferably resolved by echocardiography-guided pericardiocentesis. In patients who have recently undergone cardiac surgery and in those with neoplastic infiltration, effusive–constrictive pericarditis, or loculated effusions, fluoroscopic guidance can increase the feasibility and safety of the procedure. Surgical management is indicated in patients with aortic dissection, chest trauma, bleeding or purulent infection that cannot be controlled percutaneously. After pericardiocentesis or pericardiotomy, NSAIDs and colchicine can be considered to prevent recurrence and effusive–constrictive pericarditis.

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Introduction

The human pericardium is a sac that surrounds the heart and the roots of the great vessels. The pericardium is comprised of a double-layered serosal membrane, with a visceral layer (epicardium) that covers the surface of the heart and a parietal layer that coats the inner surface of the sac. The external surface of the pericardium consists of fibrous connective tissue fused to the parietal serosa[1]. This construction forms the pericardial space, which contains pericardial fluid comprised predominantly of plasma filtered through the epicardial capillaries and probably the parietal layer of the pericardium (Fig. 1a). The underlying myocardium also contributes a small amount of interstitial fluid[2]. Under physiological conditions, the pericardial space contains 20–60 ml of fluid drained by the lymphatic capillary bed. The volume of fluid is determined by the equilibrium between production and drainage[3].

Cardiac tamponade is a potentially life-threatening emergency, characterized by progressive intrapericardial accumulation of fluid (or pus, blood, clots or air) leading to increased intrapericardial pressure and compression of the heart. Diastolic filling and cardiac output are subsequently impaired, resulting in haemodynamic compromise, typical obstructive circulatory shock[4] or even cardiac arrest[5,6] (Fig. 1b).

Pericardial diseases of any aetiology can cause cardiac tamponade but certain entities have a higher risk of evolution towards circulatory shock (especially tuberculous pericarditis and malignancies)[6–9] (Table 1). Depending on the aetiology, pericarditis (inflammation of the pericardial sac, which can be caused by a bacterial or viral infection, chest injury, medications or concomitant conditions) is often initially associated with a small pericardial effusion (accumulation of excess fluid in the pericardium) that can increase over time and progress to cardiac tamponade. In patients with massive intrapericardial bleeding (for example, as a consequence of myocardial or coronary artery perforation, extension of aortic dissection, or trauma), acute cardiac tamponade develops in minutes and is characterized by rapidly evolving, dramatic clinical haemodynamic deterioration leading to cardiac arrest[10,11] (Fig. 2a). Pericardial effusion in individuals with severe pulmonary hypertension is a unique, albeit important, subset that can be difficult to manage as pericardiocentesis in these individuals carries the risk of acute right ventricle failure and can be fatal[12]. If pericardial effusion occurs slowly, with clinical worsening over several days or weeks (Fig. 2b), the compressive effects should be considered as a continuum, with no simple threshold to identify patients in critical condition requiring immediate pericardial drainage[9,13], and these patients need to be closely monitored to determine if and when intervention is needed.

In this Primer, we discuss the epidemiology and pathophysiology of cardiac tamponade as well as the clinical signs and imaging features used in diagnosis. This information is based on the 2014 triage strategy position statement[5] and the latest (2015) guidelines on pericardial diseases from the European Society of Cardiology (ESC) Working Group on Myocardial and Pericardial Diseases[3] for the diagnosis, scoring and treatment of cardiac tamponade. We also suggest the best management options for the evacuation of pericardial fluid as well as novel strategies for the prevention of recurrence. In addition, we discuss patient quality of life in various clinical settings. Finally, we highlight gaps in our knowledge of cardiac tamponade and consider the importance of future studies, clinical trials and registries in addressing important research questions.

Epidemiology

General incidence and prevalence

To date, few reports have been published on the incidence, prevalence or exact aetiology of cardiac tamponade in the general population. Only indirect data about the epidemiology of conditions that can lead to cardiac tamponade can be found in the literature. Surprisingly, despite the fairly high frequency of pericardial syndromes in clinical practice (including acute, incessant, recurrent and chronic pericarditis, pericardial effusion, cardiac tamponade, and constrictive pericarditis)[3], the incidence or prevalence of these conditions in the general population is unknown and epidemiological data are scarce. However, epidemiological data from national inpatient sample data bases collected between 2008 and 2014 in the USA have been published[14]. Among 216 million emergency admissions in patients aged >18 years (mean age ~62 years), the incidence of cardiac tamponade was 0.05% (115,638 cases); 63.4% of these patients were white, 12.6% were Black and 7.4% were Hispanic. There was no significant difference in the male-to-female ratio (46.5% female). The reported causes of cardiac tamponade included chest trauma (2.1%), connective tissue diseases (4.0%), chronic kidney disease (18.4%), cancer (17.0%), sepsis (10.6%) and idiopathic pericarditis (3.7%). In-hospital mortality was high (14.3%) and remained so throughout the study period. Chest trauma, acute kidney injury, metastatic cancer and sepsis were significant predictors of mortality[14]. A post-mortem study focused on haemopericardium found that, among 430,000 postmortems between 1995 and 2004 in a rural English population, mortality was due to cardiac tamponade in 461 cases[15].

Risk factors

Risk factors for cardiac tamponade include pericarditis, malignancies, autoimmune conditions (systemic lupus erythematosus (SLE) and rheumatoid arthritis), cardiovascular conditions and iatrogenic (resulting from medical activity such as a treatment or diagnostic procedure) factors such as cardiovascular interventional procedures and surgery.

Pericarditis. The most commonly encountered pericardial disease in the clinic is acute pericarditis, which is the cause of 0.1% of all hospital admissions and 5% of emergency room admissions for chest pain in the USA and Europe[3]. The reported annual incidence of acute pericarditis was 27.7 cases per 100,000 of the population in emergency room and hospital admissions from an Italian community[16] but was much lower in the Finnish national registry for the years 2000–2009 (3.32 cases per 100,000 of the population)[17]. These data from Finland only include hospitalized patients and might therefore represent only a minority of cases as many patients with pericarditis are not admitted to hospital. Among individuals aged 16–65 years, the risk of pericarditis was higher in men than in women (relative risk 2.02), and the highest risk difference compared with the overall population was among young adults[17]. In a study of 7 million individuals from Danish medical data bases, a much higher annual incidence of acute pericarditis was reported (168 cases per 100,000 of the population)[18]. In this investigation, all patients with a first-time diagnosis of acute pericarditis during the period 1994–2013 were identified. Pericarditis was recorded as the primary discharge diagnosis in 79% of patients. The presence of or progression to cardiac tamponade was not evaluated[18]. This study is more representative that the Italian and Finnish studies as it was not limited to hospital admissions. A study from the USA revealed that the hospitalization rate in Medicare beneficiaries aged ≥65 years with a principal discharge diagnosis of pericarditis between 1999 and 2012 remained stable during the study period (26 per 100,000 person-years)[19]. The incidence

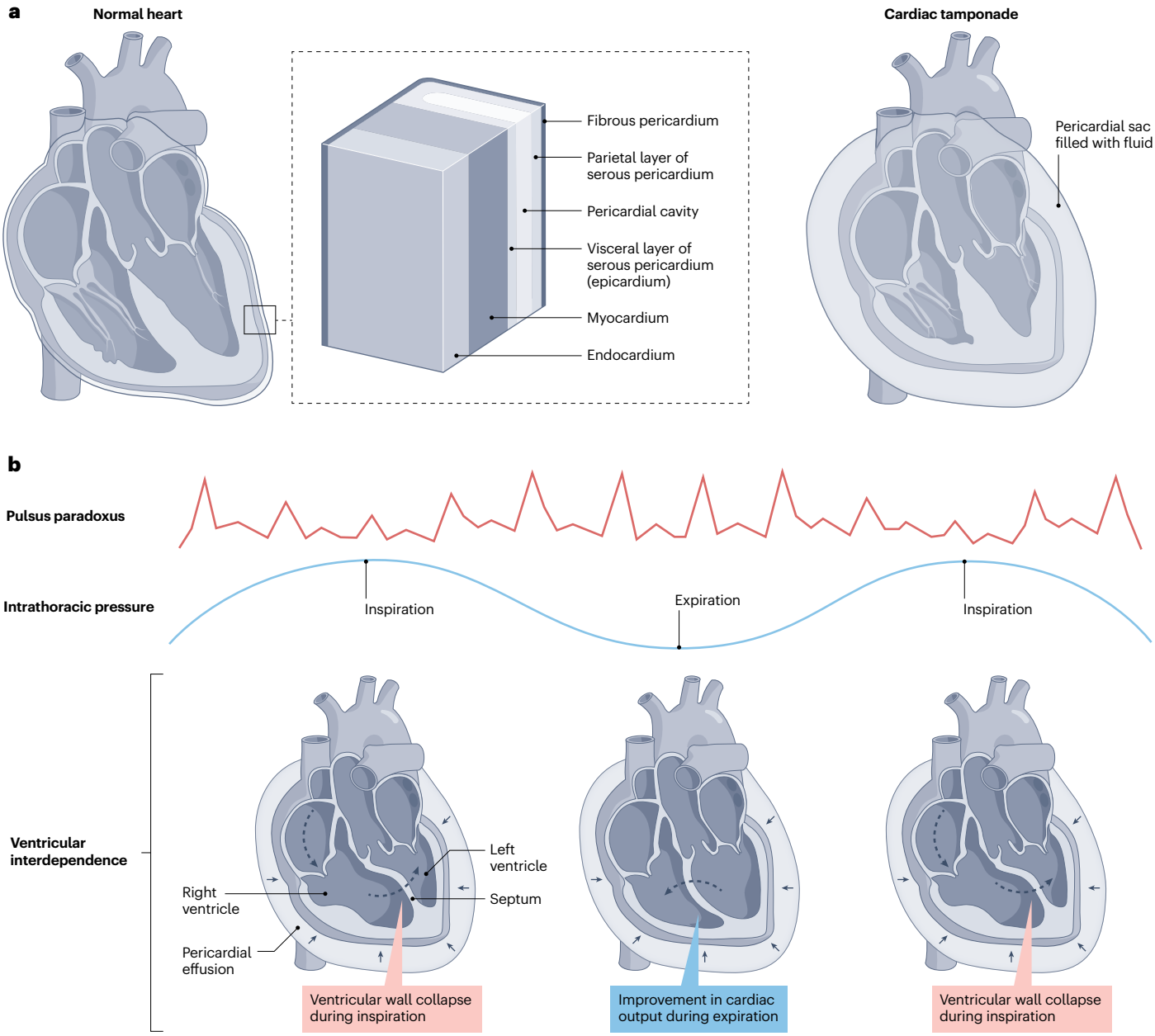

Fig. 1 | Anatomical changes to the heart during cardiac tamponade. **a**, Schematic of the heart depicting the layers of the pericardium and excessive intrapericardial pressure during cardiac tamponade. **b**, The basic pathogenetic mechanisms of cardiac tamponade. Progressive intrapericardial accumulation of fluid leads to increased intrapericardial pressure and compression of the heart. Diastolic filling and cardiac output are subsequently impaired, resulting in haemodynamic compromise, circulatory shock and, eventually, cardiac arrest. Owing to ventricular interdependence, expansion of the right ventricle during inspiration compresses the left ventricle, resulting in decreased filling and a drop in stroke volume with a decrease in systolic blood pressure (pulsus paradoxus). During expiration, the left ventricle is filled by the restoration of pulmonary venous return but the right ventricle is compressed and systemic venous return is interrupted. Part **b** adapted with permission from ref. 207, © The Authors.

of pericarditis in this study is similar to that reported by the Italian group[15] and was consistently higher in men and in very elderly patients (≥85 years of age)[19]. Adjusted all-cause mortality decreased over the study period (from 7.6% in 1999 to 5.7% in 2012 for 30-day mortality, and from 19.7% in 1999 to 17.3% in 2011 for 1-year mortality)[19]. On the basis of these studies, assuming an annual incidence of acute pericarditis of between 26 (refs. 16,19) and 168 (ref. 17) cases per 100,000 of the population, the question remains about what proportion of these patients develop pericardial effusion and cardiac tamponade.

The incidence of pericardial effusion is estimated to be around 20 cases per 100,000 population[20]. Pericardial effusion in developed countries is most frequently of idiopathic origin (up to 50% of cases),

Table 1 | Criteria for triage of patients with pericardial effusion at risk for progression to cardiac tamponade

Aetiology	Clinical presentation	Imaging
Likely to progress to cardiac tamponade		
Malignancy (2) Tuberculosis (2) Recent radiotherapy (1) Recent viral infection (1) Recurrent pericardial effusion, previous pericardiocentesis (1) Chronic terminal renal failure (1) Immunodeficiency or immunosuppression (1) Iatrogenic haemopericardium (2) Severe trauma with haemopericardium (3) Rupture of the free wall after acute myocardial infarction (3) Type A aortic dissection with haemopericardium (6)	Dyspnoea or tachypnoea (1) Orthopnoea (no rales on lung auscultation) (3) Hypotension (SBP <95 mmHg) (1) Distended jugular veins (1) Progressive sinus tachycardia (1) Oliguria (1) Pulsus paradoxus >10 mmHg (2) Rapid worsening of symptoms (2)	Cardiomegaly on chest radiography (1) Electrical alternans on ECG (0.5) Microvoltage on ECG (1) Circumferential pericardial effusion (>2 cm in diastole) (3) Moderate pericardial effusion (1–2 cm in diastole) (1) Right atrial collapse >1/3 of cardiac cycle (1) IVC >2.5 cm, <50% inspiratory collapse (1.5) Right ventricular collapse (1.5) Left atrial collapse (2) Mitral and/or tricuspid respiratory flow variations (1) Swinging heart (1)
Rarely progressing to cardiac tamponade		
Early and late pericarditis Dressler syndrome in acute myocardial infarction (0) Autoreactive chronic pericardial effusion (0) Any other aetiology of chronic pericardial disease (that is, cholesterol pericarditis, chylopericardium) (0) Hypothyroidism or hyperthyroidism (–1) Systemic autoimmune disease (–1)	Low-grade fever (0.5) Distant heart sounds (0.5) Pericardial chest pain (0.5) Pericardial friction rub (0.5) Normal blood pressure (–1) Slow evolution of the disease (–1)	Normal chest radiograph (–1) Normal ECG (–1) Moderate pericardial effusion (1–2 cm in diastole) (1) Small pericardial effusion (<1 cm in diastole), no trauma or recent interventional procedure (–1)
Never progressing to cardiac tamponade		
Pericardial transudates in heart failure or pulmonary hypertension (0) Pericardial transudates in the last trimester of normal pregnancy (0)	Pulmonary oedema (0)	Pericardial effusion only in systole (0)

Numbers in parentheses are points in the scoring system for the triage of patients with cardiac tamponade. A total score >6 indicates a need for immediate drainage of pericardial effusion. ECG, electrocardiography; IVC, inferior vena cava; SBP, systolic blood pressure. Adapted with permission from ref. 5, Oxford University Press.

although cancer (10–25%), infections (15–30%), iatrogenic causes (15–20%) and connective tissue diseases (5–15%) are also common causes. Tuberculosis is the most frequent cause of pericardial effusion in developing countries (>60%), where it is endemic[21,22].

Pericardial effusion is not uncommon in end-stage renal disease (ESRD)[3]. Two entities unique to patients with kidney disease are uraemic pericarditis (which develops before or within 8 weeks of initiation of dialysis) and dialysis-associated pericarditis (which occurs in patients on dialysis for more than 8 weeks). The prevalence of asymptomatic pericardial effusion, which could be from either pericarditis or volume overload alone, has been reported in 70–100% of these patients[23]. Initial studies reported the incidence of cardiac tamponade in up 20% of patients with dialysis-associated pericarditis[24].

A rising prevalence of ESRD in the modern era of renal replacement therapy has led to an increase in ESRD-related pericardial syndromes, yet little is known about the prevalence and implications of pericardial effusion in this setting[25,26]. A 2020 retrospective chart review of 2,820 individuals older than 18 years with known ESRD who were undergoing outpatient evaluation for renal transplantation at Mayo Clinic Arizona (2001–2015) reported a prevalence of moderate-to-large effusions of 1.9% and cardiac tamponade in 7 patients[26].

Cancer or infection account for 15–50% of cases of pericardial effusion resulting from pericarditis[27,28]. A study published in 2019 evaluated the outcome of idiopathic, chronic (>3 months), large pericardial effusions (>20 mm on echocardiography) without initial evidence of pericarditis in 100 patients. These pericardial effusions were usually benign, in most cases they reduced in size during follow-up (mean 50 months) and complete regression occurred in ~40% of cases. The risk of cardiac tamponade was 2.2% per year[29]. A study conducted in 1999 (study period 1977–1992) reported occasional patients with large, initially asymptomatic effusions[30]. Patients with suspected idiopathic chronic pericardial effusions were prospectively enrolled and followed up for 18 months to 20 years (median, 7 years). Of 1,108 patients with pericarditis, 461 had a large pericardial effusion and 28 of these patients were included in the study. Overt tamponade was present in 8 (29%) patients and 7 of the 8 patients had pericardial effusion for 1–8 years (median 4 years). During follow up, 10 patients died (due to cancer, chronic kidney disease, coronary artery disease, stroke or dementia) and 1 patient was lost to long-term follow up. Among the remaining 17 patients, pericardial effusion was absent in 14 patients, mild in 2 patients and moderate in 1 patient; cardiac tamponade developed in 1 patient after 2 years[30]. The patient population in these two studies differs in some points. The 1999 study included more women (67% compared with 54% in the 2019 study) and the sum of anterior and posterior echo-free spaces at end-diastole ranged from 23 to 54 mm, while the median size of the effusion in the 2019 study was 25 mm. Furthermore, overt tamponade was present in 29% of cases in the 1999 study and the follow-up was longer.

A prospective, registry-based, case-control study of patients with the congenital condition pectus excavatum showed that 13.9% of 86 control individuals who underwent chest CT for cardiovascular disease (but did not have pectus excavatum) had a small pericardial

effusion[31]. Pericardial effusion was significantly more common among patients with pectus excavatum than controls (odds ratio 10.91). The authors concluded that the absence of adverse pericardial events at follow-up suggested a good prognosis for these effusions[31].

Cardiac tamponade has been reported in <15% of patients with idiopathic acute pericarditis and in up to 60% of those with bacterial or neoplastic forms[32]. In a systematic review of publications on recurrent pericarditis published between 1966 and 2006, the rate of cardiac tamponade among patients with idiopathic recurrent pericarditis was 3.5%, giving an estimated incidence of ~1–6 cases per 100,000 population. Most of these cases of cardiac tamponade occurred early in the course of the disease[33].

Malignancy. In developed nations, cardiac tamponade is most frequently found in patients with cancer[34–38], although the exact prevalence is unknown. Cardiac tamponade can occur in the presence of solid tumours (most commonly lung and breast cancers, adenocarcinoma, oesophageal squamous cell carcinoma, melanoma, thymic carcinoma and, rarely, germ cell, renal, or bladder cancer and Ewing sarcoma) or haematological malignancy (usually leukaemia and non-Hodgkin and Hodgkin lymphomas and, rarely, acute and chronic myeloid leukaemia and myelodysplastic syndrome)[18,39–43].

Cardiac tamponade can occur as the result of the malignancy per se[44] or the treatment being received (chemotherapy or radiotherapy). A retrospective analysis of 1,207,580 adult patients (age ≥18 years) with lung cancer in the 2016–2018 Nationwide Inpatient Sample identified 7,105 (0.6%) individuals who developed cardiac tamponade. This outcome was more common in men and among patients who received radiation therapy (0.9% versus 0.7%)[45]. In a study conducted in 2015 of 1,645 patients with cancer who were referred for pericardial effusions, 212 (13%) underwent percutaneous pericardiocentesis — 186 (88%) were exposed to chemotherapy (doxorubicin, cyclophosphamide and carboplatin) and 33 (16%) received radiation therapy to the mediastinum within 1 year before the procedure[46]. Radiation-induced cardiovascular diseases, among which are pericardial syndromes, are well described as a late effect in patients with cancer treated with radiation therapy. Exposure to ≥250 mg/m^2 of anthracyclines increased the relative hazard twofold to fivefold, while cardiac radiation exposure of ≥1,500 cGy increased the relative hazard by twofold to sixfold compared with survivors that had not undergone radiation therapy[47]. Radiation therapy is known to be associated with acute pericarditis and, subsequently, with pericardial effusion leading to cardiac tamponade[47].

Autoimmune diseases. Cardiac involvement is not uncommon in systemic inflammatory diseases. Several groups have reported on the incidence of cardiac tamponade in patients with SLE at their centres. One group found that 16.4% of 690 patients had SLE-related pericardial effusion and 1.5% had cardiac tamponade[48]. Mortality was higher among patients with than in those without pericardial effusion (30.1% versus 11.3%; $P < 0.001$)[48]. A group from India reported that pericarditis and cardiac tamponade were diagnosed in 25.4% and 5.9%, respectively, of 409 patients with SLE[49,50].

Pericardial effusions are usually clinically silent in rheumatoid arthritis[51] and are often identified on autopsy[52] (11–50% in necropsy studies). Asymptomatic pericardial effusions were reported in 20.3% of 87 patients with rheumatoid arthritis[53], predominantly in men, and coexisted with pleural effusions. Progression of these effusions to tamponade is described in case reports[54].

Cardiovascular conditions. Cardiac tamponade occurs in <1% of patients with fibrinolytic-treated ST-segment elevation myocardial infarction and is associated with increased 30-day mortality[55]. According to an analysis of data from over 100,000 patients, increasing age, anterior infarct location, female sex and increased time from

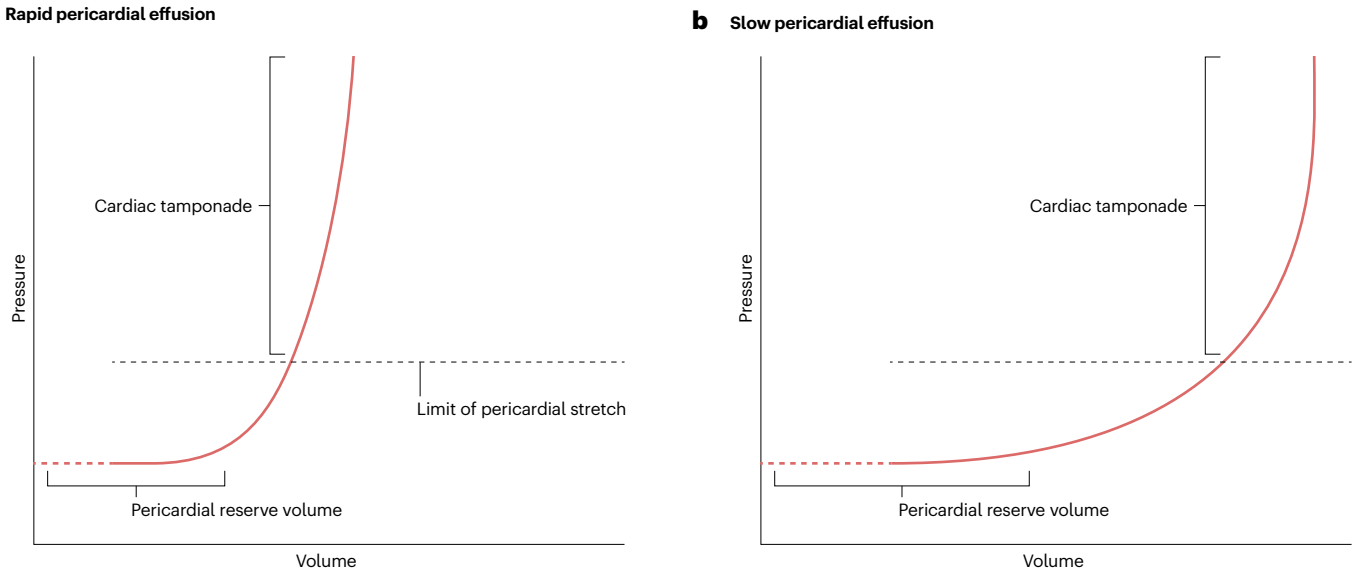

Fig. 2 | Pressure–volume curves depicting acute and chronic pericardial effusion. a, Rapid fluid accumulation in iatrogenic acute pericardial effusion due to, for example, perforation of coronary arteries during percutaneous coronary intervention, myocardial perforation during endomyocardial biopsy or pacemaker lead placement, electrophysiology procedures or trauma. When the effusion reaches the maximum pericardial reserve volume, any further increase in fluid and, consequently, in the rate of expansion will exceed the limit of pericardial stretch. **b**, Slow fluid accumulation in chronic pericardial effusion[10,88]. Pericardial stretching over an extended period of time results in a shift in the pressure–volume curve to the right (stress relaxation). Therefore, slowly developing effusions might not necessarily result in cardiac tamponade. Reprinted with permission from ref. 208, Oxford University Press.

symptom onset to treatment were significant independent predictors of tamponade[55]. Importantly, clinicians should consider cardiac tamponade due to pericardial effusion as a potential cause of hypotension in patients with acute ST-segment elevation myocardial infarction. Post-myocardial infarction pericarditis occurs with an incidence of <5% in developed countries and may present as early infarct-associated pericarditis (within 5 days after an acute event) or late post-myocardial infarction pericarditis (also known as Dressler syndrome; presents 2–8 weeks after infarction). Delayed angioplasty is a major risk factor for pericarditis. Cardiac tamponade is a rare complication in both[56].

The incidence of cardiac tamponade has been reported to be 8–31% in patients with acute aortic dissection[57–60]. However, many of these patients die before reaching hospital and before a diagnosis can be made. In the large cohort of the International Registry of Acute Aortic Dissection, 18.7% of 674 patients (mean age 61.8 years) had cardiac tamponade as a life-threatening complication of acute type A aortic dissection[60]. Tamponade complicating aortic dissection was associated with poor in-hospital outcomes and significantly increased mortality[60].

Iatrogenic factors. Post-cardiac injury syndrome can manifest in a variety of circumstances, with one common feature — previous injury to the myocardium with blood in the pericardial cavity (haemopericardium). The syndrome can develop after cardiac surgery (post-pericardiotomy syndrome), blunt or penetrating cardiac trauma, or perforation of the heart with a catheter.

Despite advances in cardiac surgery techniques, it remains a common postoperative complication and the cause of surgical reintervention in 0.1–6% of cases[61]. Early pericardial effusion appears in the first 48 h after surgery and is related to microvascular bleeding, while late-delayed pericardial effusion, which occurs more than 48 h postoperatively, is attributed to an inflammatory reaction of the pericardium[62,63]. Late-delayed pericardial effusion does not show specific clinical signs, which makes it more difficult to diagnose than early pericardial effusion[61]. In studies from the early 2010s of the contemporary features, risk factors and prognosis of post-pericardiotomy syndrome, the incidence of cardiac tamponade after cardiac surgery varied from 1.9%[64] (Italian study, 360 patients) to 4.3%[65] (South Korea). In a 2020 retrospective, observational cohort study of 1,460 adult patients undergoing heart valve surgery at Odense University in Denmark, the incidence of cardiac tamponade was 17%[66].

Iatrogenic cardiac tamponade can also be caused by complications of interventional procedures such as electrophysiological tests, coronary or valvular interventions, endomyocardial biopsy and pacemaker implantation[7,11,13]. The increasing use of these procedures has led to a rise in the incidence of haemopericardium. In the literature, the reported prevalence of coronary perforation as the procedural complication of percutaneous coronary intervention is 0.2–0.6%, with associated increases in mortality and in rates of pericardial tamponade and cardiogenic shock[67]. However, the incidence of these complications has decreased over the past couple of decades[67–70]. Among 389 patients undergoing transcatheter aortic valve implantation (TAVI) between 2007 and 2012, cardiac tamponade occurred in 4.3%, and mortality among these individuals was 23.5%[71]. In a more recent analysis (study period 2015–2019), cardiac perforation and tamponade occurred in 0.9% of 2,102 patients undergoing TAVI[72]. The risk of cardiac tamponade was substantially greater and nearly doubled in patients who required a permanent pacemaker after TAVI versus those who did not (1.6% versus 0.8%); among 54,317 unweighted hospitalizations for TAVI, 5,639 (10.4%) required a pacemaker[73]. Female sex was independently associated with an increased risk of pericardial effusion and cardiac tamponade[73]. Ablation of atrial fibrillation can also be complicated by cardiac tamponade. In a study of 34,943 ablation procedures in 25,261 patients at 19 centres, the incidence of tamponade was 0.84%[74]. The risk of tamponade was almost twofold higher in women than in men, and high-volume centres were associated with a lower risk of this outcome[74]. The reported rate of cardiac tamponade was similar (0.8%) in a single-centre study of 1,500 catheter ablations[13].

Cardiac tamponade can be precipitated by the erroneous use of various medications used to treat other disorders[3]. Intravenous loop diuretics can magnify the effects of a pre-existing effusion (so-called low-pressure tamponade) and some, such as β-blockers, impair responses that can help compensate for a significant effusion. Others, such as anticoagulants and thrombolytics, can increase the size of an effusion or occasionally cause one de novo[3].

Mechanisms/pathophysiology

Anatomical and physiological role of the pericardium

The anatomy of the pericardium supports its most important functions — stabilizing the position of the heart, reducing friction by lubricating the moving surfaces of the heart, and equalizing gravitational and hydrostatic forces mediated by the pericardial fluid[75]. The pericardium also provides mechanical support, mainly through the parietal pericardium, by limiting cardiac distension and facilitating ventricular coupling and interaction[76]. Ventricular coupling (or ventricular interdependence) occurs when the function of one ventricle is altered by changes in the filling of the other ventricle. By acting as a mechanical barrier to infection, the pericardium also has metabolic and immunological functions. Substances produced by the mesothelial cells of the parietal serosa, such as prostacyclin, eicosanoids and prostaglandin E2, regulate sympathetic neurotransmission and myocardial contractility and can affect epicardial coronary arterial tone[77,78].

The movement of fluid through the visceral and parietal layers of the pericardium is the result of hydrostatic and/or osmotic pressure equilibrium between the microvasculature and the cavity, with a net pressure difference of 2–10 mmHg, which drives the fluid from the epicardium towards the pericardial cavity[3,79]. Therefore, total pericardial volume includes not only the pericardial fluid but also cardiac volume and the volume of the intrapericardial portions of the great vessels. Under physiological conditions, the pericardium can stretch to accommodate changes in cardiac volume but, because of its relatively inelastic and non-compliant structure, becomes increasingly inflexible when the reserve volume is exceeded[75,80,81]. Normal pericardial pressure is best thought of as a contact pressure between the parietal and visceral pericardium, at least regarding its influence on cardiac filling pressure, and was quantified in animal models during the 1980s and 1990s[82,83].

Analysis of samples from 120 consecutive patients who underwent elective open-heart surgery showed that pericardial fluid is rich in nucleated cells, protein, albumin and lactate dehydrogenase, at concentrations consistent with inflammatory exudates in other biological fluids[84]. The Light criteria, which were originally developed for pleural effusions, have traditionally been used to characterize pericardial effusions in transudates and exudates[85,86]. However, we do not recommend the use of the Light criteria to interpret pericardial fluid as they are not validated in this setting. In fact, according to these criteria, normal pericardial fluid would almost always be erroneously interpreted as an inflammatory exudate. Speculatively, lactate dehydrogenase in particular could be released by mesothelial cells, which are abundant in normal pericardial fluid.

Pathophysiology of cardiac tamponade

Accumulation of pericardial fluid, pus, blood, clots or air can lead to a rapid (Fig. 2a) or slow (Fig. 2b) increase in intrapericardial pressure and compression of the heart resulting in chronic venous congestion, hypotension, circulatory shock and, eventually, cardiac arrest[75,87,88]. When a pericardial effusion reaches the maximum pericardial reserve volume (the volume at which the pericardium starts to expand), any further increase in volume will soon pass the limit of pericardial stretch[89,90] (Fig. 2). Normally, the pericardium is able to stretch if the effusion develops slowly over time, but the stretching capacity is determined by its histological composition (proportion of collagen and elastic fibres) and the presence of inflammatory or neoplastic infiltrate and is dependent on the effusion accumulation rate. At the limit of pericardial stretch, intramyocardial volume is competing with the intrapericardial content for the fixed, total pericardial volume. As summarized by Spodick[76,89], the stiffness of the pericardium determines the level of fluid increase that triggers cardiac tamponade, with an initial slow increase followed by an exponential increase. Therefore, cardiac tamponade is a 'last-drop' phenomenon, where the last increase in pericardial fluid leads to critical cardiac compression and the first decrease during drainage produces the greatest relative decompression[91].

In an acute situation, depending on the aetiology, fairly small pericardial effusions (<250 ml) can cause severe cardiac tamponade[92]. By contrast, large but slowly developing effusions of 1,000–2,000 ml might not result in overt cardiac tamponade.

The most common reasons for an increase in pericardial pressure, which might result in cardiac tamponade, are intrapericardial fluid accumulation, increased cardiac chamber volume or increased pericardial stiffness. The most important adverse effects on the heart include the aforementioned compressive effect, which limits filling of the heart during diastole, as well as elevated diastolic filling pressures and decreased stroke volume and cardiac output, which can rapidly become life threatening if not treated or if no compensatory mechanisms are activated[76,93].

Cardiac tamponade is a haemodynamic event that involves an equal increase in atrial and pericardial pressures (although intermediate stages occur where equality is not necessarily present), a raised expiratory decrease in aortic systolic pressure and arterial hypotension[89]. Owing to its thinner wall, the right ventricle is more readily affected than the left ventricle by the increased pericardial pressure during pericardial effusion. Pressure in the right ventricle is overridden by the sudden increase in pericardial pressure caused by the rise in ventricular volume in early diastole, such that the right ventricle might even collapse[94,95], an event that specifically defines advanced pericardial tamponade[89,96]. However, whether the volume of the right ventricle actually decreases is unclear owing to the difficulty in quantifying its volume.

As the heart is compressed throughout the cardiac cycle during tamponade, systemic venous return is impaired. Right atrial and right ventricular collapse results in left ventricular restriction due to ventricular interdependence when the total volume of the heart chambers is fixed and any change in the volume of one side of the heart causes the opposite changes in the other side[97–99]. In cases of compressive pericardial effusion, expansion of the right ventricle during inspiration compresses the left ventricle, resulting in decreased filling and a drop in stroke volume with a decrease in systolic blood pressure (SBP), termed pulsus paradoxus, of >10 mmHg (ref. 98). During expiration, the left ventricle is filled again by the restoration of pulmonary venous return, but the right ventricle is compressed and systemic venous return is interrupted.

The haemodynamic spectrum ranges from preclinical tamponade, when pericardial pressure is equal to right atrial pressure but lower than left atrial pressure, to incipient cardiac tamponade, when pericardial pressure is equal to left atrial pressure[100]. Moderate cardiac tamponade is when the mean pericardial pressure is >10–12 mmHg, an increased jugular pulse is detectable[101–103] and compression of the right ventricles can be detected[103]. Further elevation of pericardial pressure causes advanced tamponade (pulsus paradoxus, tachycardia, very low stroke volume and blood pressure)[89,97,98].

In pure (non-traumatic, non-haemorrhagic) cardiac tamponade, early diastolic filling is markedly reduced because of compression around the heart. Therefore, early diastolic mitral or tricuspid valve inflow (E velocity) is reduced. Diastolic flow in the hepatic vein is also reduced with prominent diastolic flow reversal. In patients who develop effusive–constrictive pericarditis, the mitral inflow filling pattern is similar to that of constrictive pericarditis with increased early diastolic filling[104]. Utilizing comprehensive echocardiography, a study found that 16% of patients had effusive–constrictive pericarditis after pericardiocentesis (aspiration of fluid from the pericardial space)[105].

These individuals had a higher incidence of hospitalization compared with patients who did not have effusive–constrictive pericarditis[105]. However, contrary to previous studies[106], in which a high incidence of pericardiectomy was reported, pericardiectomy was seldom necessary as constrictive haemodynamics caused by pericardial inflammation usually resolved spontaneously or with anti-inflammatory medication[105].

Molecular mechanisms

The inflammasome was first reported in 2002 (ref. 107) and has since been a major focus of research on innate immunity[108–110]. The role of inflammasome activation has been investigated in the pathological progression of various cardiovascular diseases. The NACHT, LRR and PYD domains-containing protein 3 (NLRP3) inflammasome is a protein complex that acts as a platform for the rapid induction of an inflammatory response to infection or sterile injury. NLRP3 induces not only the production of pro-inflammatory cytokines, by promoting the cleavage and release of IL-1 family cytokines, but also a specific programmed cell death pathway known as pyroptosis. The NLRP3 inflammasome is a research area of great promise for idiopathic and post-injury pericarditis[111] and could also be relevant in patients with overt cardiac tamponade due to idiopathic effusive–constrictive pericarditis. However, the significance of NLRP3 has not been demonstrated in tamponade of other aetiologies as suitable animal models of pericarditis are lacking.

In 2021, a study reported on a new experimental model of acute pericarditis in mice through the intrapericardial injection of zymosan A, an activator of the NLRP3 inflammasome[112]. Zymosan A causes the classical features of pericardial inflammation, including pericardial effusion, pericardial thickening, upregulation of IL-1α and IL-1β, and increased expression of apoptosis-associated speck-like protein as an unambiguous marker of NLRP3 inflammasome activation. Anti-inflammatory medications, such as ibuprofen (an inhibitor of prostaglandin G/H synthase 2, also known as cyclooxygenase 2) and colchicine (an NRLP3 inhibitor), reduced pericardial effusion but not pericardial thickening. IL-1 blockade via two different IL-1 receptor antagonists — anakinra and rilonacept — significantly reduced both pericardial effusion and thickening[112]. However, to date, no promising data are available that specifically address the inflammasome or any other molecular mechanisms in the occurrence of cardiac tamponade.

Diagnosis, screening and prevention

Clinical presentation

Cardiac tamponade is a clinical emergency that should be promptly recognized (Fig. 3) as a possible cause of dyspnoea (shortness of breath or breathlessness) accompanied by elevated systemic venous pressure, tachycardia, low blood pressure and paradoxical arterial pulse in the presence of haemodynamically important pericardial effusion on echocardiography. Ultimately, cardiac tamponade is a clinical diagnosis requiring echocardiographic confirmation[113–115].

Classical symptoms and signs include dyspnoea (progressing to orthopnoea (shortness of breath or breathlessness when lying down, which necessitates sleeping in a sitting or propped-up position), weakness, fatigue, tachycardia and oliguria (urinary output <400 ml per day or <20 ml per hour)[3,5,10,89]. If cardiac tamponade is preceded by acute pericarditis, the patient might experience typical chest pain increasing on inspiration and radiating to the trapezius ridge. Local compression from the pericardial effusion can also occasionally manifest as nausea, dysphagia, hoarseness and hiccups[89]. Additional clinical manifestations depend on the aetiology; some patients with viral aetiology[116] present with right upper quadrant pain due to hepatic venous congestion and hepatomegaly.

Some but not all traditional physical findings (hypotension, increased jugular venous pressure and muffled heart sounds)[117] are present in a substantial portion of patients with echocardiographic evidence of cardiac tamponade. In acute cardiac tamponade, SBP is <90 mmHg but, in subacute cases, blood pressure might be only slightly reduced, and patients with hypertension have normal to mildly elevated blood pressure (relative hypotension)[118]. Signs of advanced cardiac tamponade reflect varying degrees of reduced cardiac output and circulatory shock (rapid breathing, sweating, cool extremities, peripheral cyanosis and a decline in consciousness). Jugular venous distension is striking but can be less prominent in patients with hypovolaemia or if pericardial effusion accumulates slowly[91,117,118]. Pulsus paradoxus[93,96] can be detected during blood pressure measurement as the difference between the SBP at which Korotkoff sounds (audible noises used to measure blood pressure using a stethoscope) are first audible and the SBP at which they are audible through the whole respiratory cycle[119–121] (Fig. 3a). Large pericardial effusions can compress the base of the lung, resulting in Bamberger–Pins–Ewart sign (a dullness on percussion in the precordium and under the left scapula), which is present in a subset of patients with possible cardiac tamponade[92]. In addition, fever is a non-specific sign that can be associated with an infectious or immune-mediated aetiology of pericarditis. The most widely known clinical signs of cardiac compression described by Beck in 1935 (ref. 122) (hypotension, increased jugular venous pressure and distant heart sounds) are still frequently quoted as the clinical diagnostic criteria for cardiac tamponade; this triad was seen in patients undergoing surgery for intrapericardial haemorrhage due to trauma or myocardial or aortic rupture[102,123]. However, many studies and clinical observations have demonstrated that the triad is not sensitive or specific for cardiac tamponade. In a retrospective study of emergency department admissions conducted in 2017, sensitivity of the Beck triad was found to be 0% (range 0–19.4%) and sensitivity for one finding was 50% (range 28–72%)[124].

The presence of pericardial effusion or cardiac tamponade is usually secondary to an underlying pathology, some of which can be life threatening such as aortic dissection or free wall rupture. The differential diagnosis of cardiac tamponade includes pulmonary embolism, type A aortic dissection without cardiac tamponade and

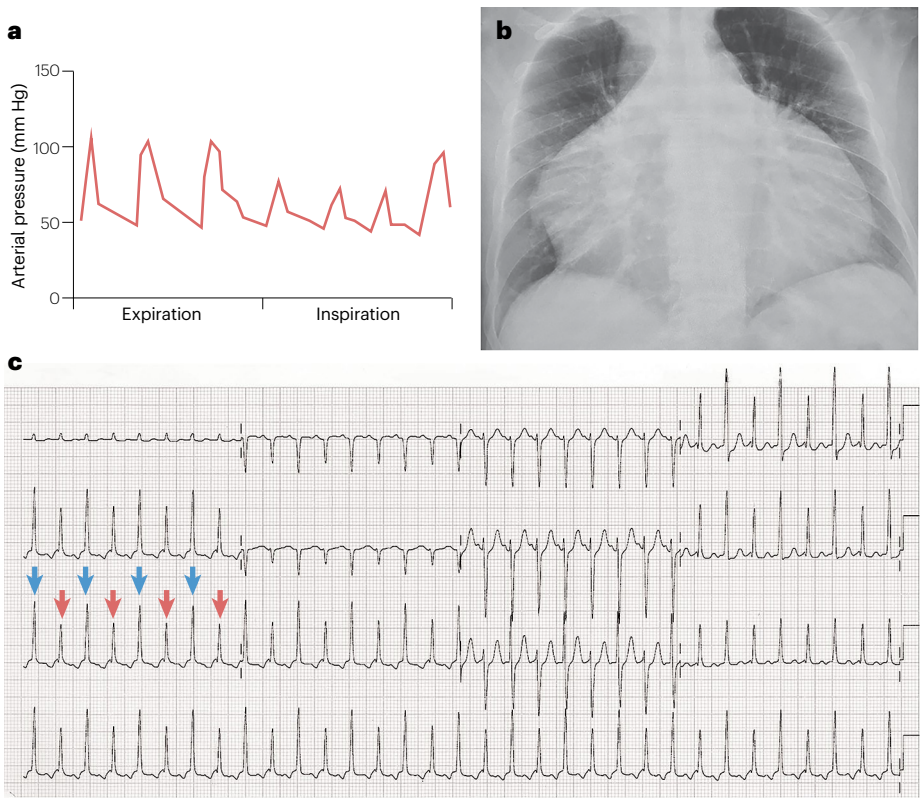

Fig. 3 | Diagnostic techniques in cardiac tamponade. a, Pulsus paradoxus: inspiratory reduction of >10 mmHg in systolic blood pressure. **b**, Chest radiograph showing cardiomegaly and a 'water bottle' shaped cardiac silhouette. **c**, Electrocardiogram showing tachycardia, low QRS voltage and electrical alternans (phenomenon of alternation of QRS complex amplitude; blue and red arrows). Part **a** reprinted with permission from ref. 10, Oxford University Press.

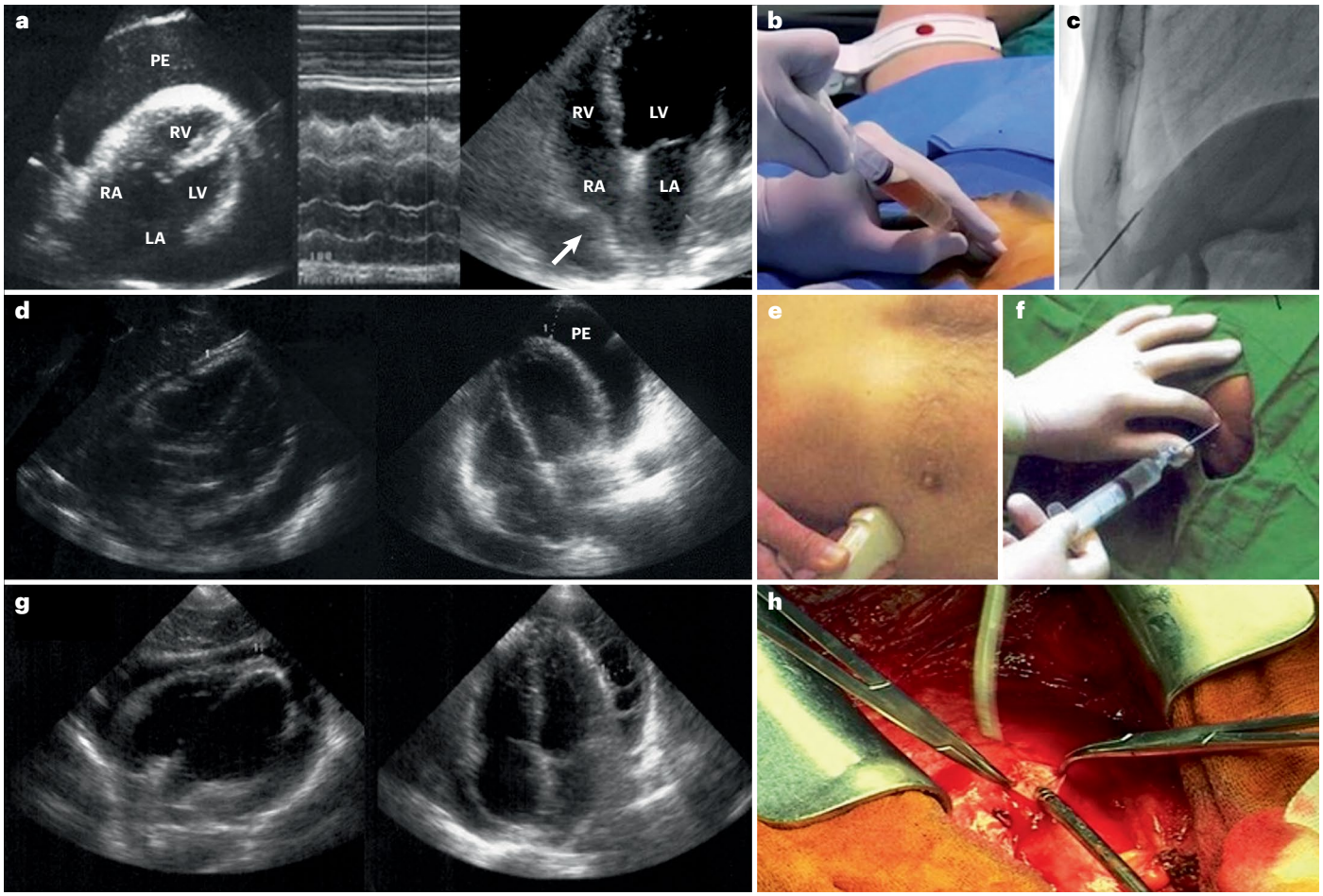

Fig. 4 | Echocardiography and pericardiocentesis in cardiac tamponade. Large pericardial effusion from the 2D subxiphoid view, M-mode view and apical long-axis view with right atrium collapse (arrow) (part **a**) and subxiphoid approach to pericardiocentesis (part **b**) guided by echocardiography and fluoroscopy (part **c**). Large separation of pericardial layers from the apical view (part **d**, left image) but very small from the subxiphoid (part **d**, right image). Echocardiographic guidance from the apical angle or view (part **e**) for pericardiocentesis from the intercostal (apical) approach (part **f**). Loculated pericardial effusion with massive adhesions (part **g**). Surgical drainage: subxiphoid pericardiotomy (also known as sternotomy with pericardiotomy; part **h**). LA, left atrium; LV, left ventricle; PE, pericardial effusion; RA, right atrium; RV, right ventricle. Reprinted with permission from ref. 10, Oxford University Press.

acute myocardial infarction involving the right ventricle. In subacute onset effusive–constrictive pericarditis, congestive heart failure and advanced liver cirrhosis should be excluded. In contrast to patients with heart failure, those with cardiac tamponade do not have pulmonary crackles or pulmonary oedema — a condition caused by excess fluid in the lungs.

Diagnostic tools and modalities

Echocardiography. Before the introduction of echocardiography, the detection of pericardial effusion was challenging. Indeed, assessment of pericardial effusion was one of the first clinical applications of echocardiography in 1965 (ref. 125). Over the past six decades, echocardiography has become the diagnostic modality of choice, not only for the detection of pericardial effusion but also for the diagnosis of cardiac compression and to guide pericardiocentesis[126,127].

In the 2015 ESC guidelines on pericardial diseases, echocardiography is recommended as the single most important diagnostic tool for the detection of cardiac tamponade[3]. Two-dimensional echocardiography can detect diastolic right ventricular and atrial wall compression, which occurs when intrapericardial pressure increases in cardiac tamponade (Supplementary Video 1). In the 1970s, animal models established ventricular interdependence as the most characteristic haemodynamic feature of cardiac compression seen in cardiac tamponade and constrictive pericarditis[128,129]. Both M-mode and Doppler echocardiography detect ventricular interdependence by demonstrating respiratory variation in ventricular filling[126,130]. M-mode echocardiography provides evidence of right ventricle collapse in early diastole and pericardial effusion. Pulsus paradoxus can be easily detected as a characteristic ventricular septal motion by real-time imaging.

In most cases of cardiac tamponade, pericardial effusions are moderate to large (Fig. 4). A swinging, pendular motion of the heart within the pericardial fluid is a common finding[102,131] (Supplementary Video 2). Other major echocardiographic findings include collapse of the right atrium during late diastole (Fig. 4a and Supplementary Video 1),

collapse of the right ventricle during early diastole, compression of the left atrium and, rarely, the left ventricle (Supplementary Video 3 and Supplementary Video 4), respiratory variations in flow velocities of cardiac chambers, expiratory diastolic flow reversal (<50% reduction in the diameter of the dilated inferior cava vein during inspiration)[3,5,10,89,130] in the hepatic veins, and congestion of the hepatic veins and inferior vena cava. However, in patients with pulmonary hypertension or other conditions causing right ventricular hypertrophy or elevated right ventricular diastolic pressure, collapse of the right ventricle during early diastole can be absent.

Echocardiography is useful for the differential diagnosis of effusive–constrictive pericarditis, cardiac tamponade and constrictive pericarditis (Fig. 5). A Mayo Clinic study[104] compared echocardiography findings obtained between 2002 and 2016 of 22 patients (predominantly men, 64%) diagnosed with effusive–constrictive pericarditis who had persistently elevated jugular venous pressure after pericardiocentesis, 30 patients with constrictive pericarditis and 30 patients with cardiac tamponade with normalized venous pressure after pericardiocentesis (Fig. 5). Even before pericardiocentesis, effusive–constrictive pericarditis had unique echo-Doppler features (higher medial and lateral e′ velocities; Fig. 5) that distinguished it from both constrictive pericarditis and cardiac tamponade. Inspiratory and expiratory mitral E-to-A ratios were higher in effusive–constrictive pericarditis than in cardiac tamponade but lower than in constrictive pericarditis. Hepatic vein diastolic reversal velocities decreased in cardiac tamponade and remained unchanged in effusive–constrictive pericarditis. Three patients (all in the effusive–constrictive pericarditis group) required pericardiectomy for constrictive pericarditis during follow-up (median 481 days). Effusive–constrictive pericarditis occurred in 8% of patients undergoing pericardiocentesis for cardiac tamponade, a group that is considered to be at high risk of requiring pericardiectomy[104].

Electrocardiography. Electrocardiographic evidence of cardiac tamponade includes low QRS voltage and electrical alternans (Fig. 3b). After drainage of pericardial effusion, normalization of the QRS amplitude can be delayed but this finding is by no means consistent[132]. Atrial arrhythmias as well as widespread ST-segment elevation with or without PR depression have been reported in the setting of acute pericarditis and in patients with pericardial effusions[14].

Chest radiography. In patients with a large effusion, the cardiac silhouette has a typical ‘water bottle’ shaped appearance (Fig. 3c). This simple sign in the appropriate clinical context (a symptomatic patient with a large pericardial effusion) has a high sensitivity for the diagnosis of cardiac tamponade but does not determine the urgency of pericardiocentesis. Furthermore, cardiomegaly of other aetiologies cannot be ruled out. In patients with pericardial effusion or cardiac tamponade, the lungs can appear dark on the chest radiograph, indicating reduced pulmonary blood volume resulting from an imbalance between right-sided and left-sided cardiac output. If radiographic images have good penetration in the lateral view, pericardial fluid suggested by lucent lines within the cardiac shadow (epicardial fat pad sign) can be used for fluoroscopic guidance of pericardiocentesis in the catheterization laboratory[133–135].

Cardiac CT and cardiovascular MRI. These modalities are very rarely needed in the clinical diagnosis of cardiac tamponade except to confirm aetiology in cases of chest trauma or where there is a high suspicion of aortic dissection[129,136–139]. CT and MRI provide excellent

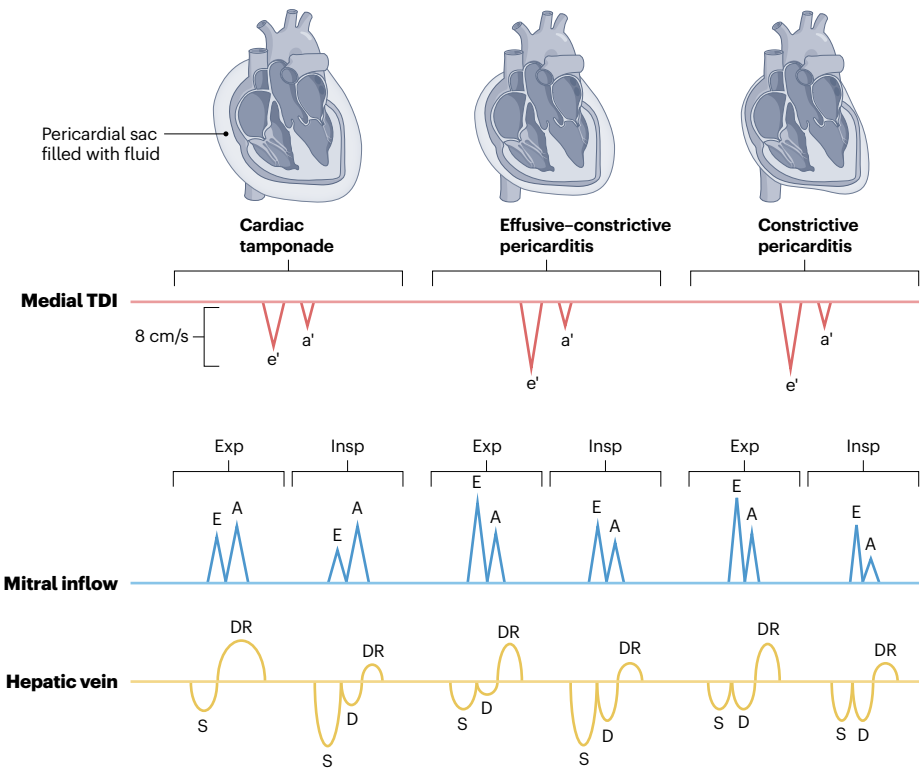

Fig. 5 | Echocardiography in the differential diagnosis of cardiac tamponade. Schematic of mitral annulus tissue Doppler imaging (TDI), mitral inflow and hepatic vein Doppler velocities in cardiac tamponade, effusive–constrictive pericarditis and constrictive pericarditis. D, diastolic forward flow; DR, diastolic flow reversal; Exp, expiration; Insp, inspiration; S, systolic forward flow. Adapted with permission from ref. 104, Oxford University Press.

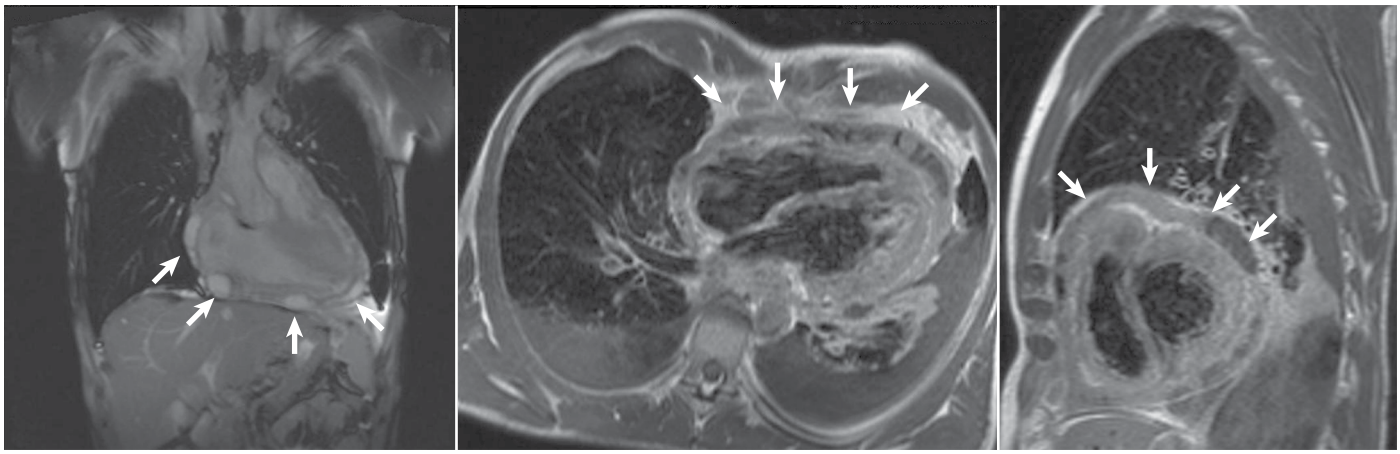

Fig. 6 | Cardiac MRI in assessment of pericarditis. Cardiac MRI views of the heart with the inflamed pericardium shown by delayed enhancement (arrows).

delineation of the pericardial anatomy and are sensitive, non-invasive methods of evaluating loculated or haemorrhagic pericardial effusion, constrictive pericarditis, pericardial thickening, pericardial masses, and congenital anomalies[130,140]. Right ventricular wall flattening and pericardial thickening correlate with haemodynamically significant pericardial effusion, and coronary sinus compression can be an early sign of cardiac tamponade on CT. Furthermore, CT can be used to determine the feasibility of percutaneous pericardiocentesis in loculated or complex effusions[130] and is particularly sensitive in identifying pericardial calcification[130]. MRI provides information about the extent of pericardial disease and defects in surrounding structures and enables accurate measurement of pericardial and related structures. MRI also provides superior tissue characterization, including the presence and extent of pericardial inflammation[141] (Fig. 6), and enables the entire chest to be examined and associated abnormalities in the mediastinum and lungs to be detected owing to the greater field of view than that of echocardiography[142–145].

Cardiac catheterization and invasive haemodynamics. These procedures allow the evaluation of heart function[146] and can be considered in cardiac tamponade when clinical examination and non-invasive imaging are inconclusive and in patients who have complex haemodynamic disorders[10,32,147]. Cardiac catheterization reveals elevated right atrial pressure, which is visible on the right atrial pressure curve as a prominent x descent and the unique finding in the jugular venous pulse wave, namely an absent y descent, in distinction to the presence of this feature in constrictive pericarditis (because early diastolic blood flow from the right atrium to the right ventricle is impaired by the compressive effect of the surrounding pericardial fluid). Diastolic pressures in all ventricles are usually 15–25 mmHg. A 'dip-and-plateau' configuration is not observed for ventricular diastolic pressure, which is elevated in early diastole and continues to rise throughout diastole[100].

Right-heart catheterization can be conducted at the same time as pericardiocentesis, allowing monitoring as the effusion is drained. After successful pericardiocentesis, if intrapericardial pressure falls to zero or becomes negative while the right atrial pressure remains elevated, the presence of effusive–constrictive pericarditis, pre-existing left-sided myocardial, tricuspid valve disease or restrictive cardiomyopathy should be considered[148].

Pericardial fluid and tissue analysis

Pericardial fluid is rich in various components, including nucleated cells, proteins and albumin as well as lactate dehydrogenase, at levels consistent with the inflammatory exudates of other biological fluids such as pleural or peritoneal fluid[84]. The normal reference values for these components of pericardial fluid were published in 2020 (ref. 84).

Diagnostic findings from routine analysis of pericardial fluid have been disappointing, limited predominantly to detecting cancer cells and bacteria. Pericardioscopy-guided extensive pericardial biopsy (of ~20 samples per patient) is a potentially powerful novel diagnostic approach but its usefulness is unclear owing to a lack of validation in a sufficient number of patients[149,150]. In this context, analysis of cytokines, inflammatory mediators, and serological and immunological markers could help identify the underlying aetiology of pericardial effusion and cardiac tamponade[151]. In a systematic review of 42 studies (mostly retrospective) performed in various countries (50% of the studies were from the USA) in the period 1972–2020, the diagnostic performance of cytology (cell analysis), histology (tissue analysis) or both was assessed[152]. Cytology was shown to be superior to histology for detecting cancer associated with pericardial effusions in most of the studies[152]. Other investigators found that the overall sensitivity of combined cytology and histology for cancer detection in pericardial effusions was 94%[153].

The International System for Reporting Serous Fluid Cytology (ISRSFC)[154] was developed to improve diagnosis, standardize reporting and facilitate communication among physicians. This system uses five reporting diagnostic categories (non-diagnostic, negative for malignancy, atypia of undetermined significance, suspicious for malignancy, and malignant – primary and secondary) linked with variable risk of malignancy[155]. A study tested the performance of this system by reclassifying 64 pericardial effusion samples using criteria defined by the system and found that the risk of malignancy was 100% for the malignant category and 0% for the negative and atypical categories[155].

Levels of tumour markers (such as adenosine deaminase, alpha-fetoprotein, the cancer antigens CA125, CA72-4, CA15-3 and CA19-9, carcinoembryonic antigen, and cytokeratin 19 fragment) in samples of pericardial fluid can also be assessed following pericardiocentesis. Although the utility of this approach in the diagnosis of neoplastic pericardial effusion is not well established, low levels of adenosine deaminase and high levels of carcinoembryonic antigen and CA72-4 are highly indicative of malignant aetiology[156,157].

Vascular endothelial growth factor is an important mediator of angiogenesis and vascular permeability produced by cells in healthy tissue but also by many tumour cells. Assessment of vascular endothelial growth factor levels in pericardial fluid offers potential as a diagnostic tool to discriminate malignant from benign effusions in patients with breast or lung cancer[158–162].

The role of pericardial pro-inflammatory mediators (IL-6 and tumour necrosis factor) and immunoregulatory cytokines (transforming growth factor-β1 and interferon-γ (IFNγ)) has been studied in neoplastic, autoreactive and viral pericarditis. Levels of IFNγ were not correlated with these aetiologies of pericarditis, whereas the pericardial-to-serum ratio of IL-6 was highest in autoreactive pericardial effusion, and the pericardial-to-serum ratios for tumour necrosis factor and IFNγ were highest in viral pericardial effusion[163]. Additional studies are needed to establish the diagnostic role of these cytokines.

Triage of patients

Prompt recognition and management of cardiac tamponade is critical but remains challenging in routine clinical practice because of the lack of validated criteria to guide clinicians in the decision-making process. The triage of patients with cardiac tamponade in the absence of circulatory shock by a three-step scoring system was proposed by the ESC Working Group on Myocardial and Pericardial Diseases[5].

The first step is to score the aetiology, the second is to score the clinical presentation and the third is to score the findings from imaging procedures (Table 1). In the absence of contraindications, a total score ≥6 indicates immediate pericardiocentesis. The ESC scoring system provides practical support to clinicians for the identification of patients needing immediate intervention or who should be transferred to a specialized institution. Although this system is based on available data and the consensus of experts, systematic, multicentre validation is still needed.

Screening

Screening for cardiac tamponade includes a thorough evaluation of each patient with pericardial disease and close follow-up of those presenting with clinical and haemodynamic worsening. Patients with large pericardial effusions (>2 cm), high fever, chest trauma and hypotension and those who do not respond to treatment with anti-inflammatory drugs are at high risk for cardiac tamponade. Prompt aetiological diagnosis and management directed towards the underlying disease, along with appropriate fluid balance and monitoring, can prevent the development of haemodynamic instability and overt cardiac tamponade[10,164].

Prevention

Not all cases of cardiac tamponade can be prevented. However, risk can be reduced by minimizing exposure to bacterial (particularly tuberculosis) or viral infections and managing underlying medical conditions such as SLE and hypothyroidism. A systematic literature review of 28 cases of cardiac tamponade following influenza infection showed that the onset of tamponade ranged from 1 day to 6 weeks. Influenza A strain was found in 78.5% of patients and B strain was found in 10.7%[165]. Vaccination is the most effective way to prevent infection and severe outcomes caused by influenza viruses[166].

Management

Without treatment, cardiac tamponade is invariably fatal. The timing of interventions is crucial — the longer the delay, the worse the outcome. Management of patients with cardiac tamponade includes pharmacological therapy, pericardiocentesis and surgery. The only effective treatment for cardiac tamponade is prompt percutaneous or surgical drainage of the pericardial effusion. Open surgery to repair the source of the effusion (for example, aortic dissection) might also be required.

Pharmacological management

Pharmacological treatment of cardiac tamponade is a temporary measure until pericardiocentesis or surgical drainage can be performed. Whether inotropic support, with or without vasodilators, is useful in hypotensive patients is debated[164]. However, volume infusion could be effective in patients with hypovolaemia and can be used as a 'bridging' therapy until pericardiocentesis can be performed[3,167]. Intravenous administration of diuretics or vasodilators is strongly contraindicated and could be fatal in patients with cardiac tamponade[3,5].

Acute pericarditis is a common cause of cardiac tamponade. In patients with this condition, the evacuation of pericardial fluid is not sufficient because pericardial fluid rapidly re-accumulates in the absence of anti-inflammatory therapy. Corticosteroids, such as methylprednisolone, are often given intravenously with doses typically ranging from 40 mg to 250 mg. However, if treatment is rapidly tapered the condition can recur. In this setting, anti-IL-1 agents can be considered, particularly in patients with fever, neutrophil leukocytosis or pleuropulmonary involvement, when C-reactive protein (CRP) level is strikingly elevated, and when corticosteroids and NSAIDs are contraindicated (for example, in patients with heart or renal failure, ischaemic heart disease, fluid overload, gastrointestinal haemorrhage, or recent surgery or those taking anticoagulants)[168].

Three anti-IL-1 agents are available — anakinra, canakinumab and rilonacept. Anakinra is a short-acting IL-1 receptor antagonist that blocks both IL-1α and IL-1β. The drug is administered daily at a dose of 100 mg subcutaneously but this dose can be doubled in cases of severe, recurrent or colchicine-resistant pericarditis[169]. In the AIRTRIP trial[169] of patients with corticosteroid dependency and recurrent colchicine-resistant pericarditis, anakinra reduced the risk of recurrence compared with placebo. Some experts consider that anakinra might be less dangerous than high-dose corticosteroids in patients with severe infection[170] or neoplasm[171]. In 2022, anakinra was used successfully to prevent cardiac tamponade in a patient with COVID-19 vaccine-related acute pericarditis[172]. Anakinra is an established drug that is known to be safe. The most common adverse effect is a short-term, usually mild reaction (redness, swelling and itching) at the injection site that responds well to topical therapy with ice and corticosteroids. Patients should be educated about the possibility of developing this reaction[168,169].

Canakinumab is a human monoclonal antibody directed only against IL-1β. Data on its use in recurrent pericarditis are limited to a few case reports and series and the efficacy of this drug, compared with anakinra, is controversial[173]. The data suggest that both IL-1α and IL-1β have a role in the induction of the inflammatory response at the pericardial tissue level, with IL-1α produced locally at the pericardial level[168]. Therefore, drugs that target both IL-1α and IL-1β should, theoretically, be most effective.

Rilonacept is a dimeric fusion protein consisting of the ligand-binding domains of IL-1 receptor protein and IL-R, which can block both IL-1α and IL-1β. The efficacy and safety of rilonacept in patients with recurrent pericarditis and elevated CRP levels were demonstrated in the RHAPSODY study[174]. Rilonacept led to rapid resolution of pericarditis and significantly reduced the risk of recurrence ($P < 001$)[174].

On the basis of this study, the FDA approved rilonacept for the treatment of recurrent pericarditis. The loading dose of rilonacept is 320 mg administered subcutaneously, followed by 160 mg weekly. Symptom relief is seen within a few days. However, no data have been published describing the effect of rilonacept in cardiac tamponade associated with acute pericarditis.

Pericardiocentesis

The best treatment for cardiac tamponade is prompt drainage of the pericardial effusion, which can be lifesaving. Importantly, the clinical presentation, aetiology, echocardiographic findings and risk–benefit ratio of the procedure must all be considered when deciding whether to drain an effusion. Patients whose condition is unstable and those with ongoing haemodynamic compromise have the highest priority for this procedure[5,175].

Aortic dissection and post-infarction rupture of the free wall are often contraindications for pericardiocentesis[3]. However, in both situations, percutaneous drainage before surgical repair can be considered when the rate of bleeding is slow. A management algorithm for percutaneous pericardiocentesis in aortic dissection has been proposed[176]. Coagulopathy, anticoagulant therapy and thrombocytopenia (<50,000 platelets/mm^3) are also contraindications to pericardiocentesis. If severe coagulation disorders are present, the procedure must be delayed until adequate blood for transfusion, platelets or coagulation factors are sourced[3,177].

Intubation and ventilation during preparation for pericardiocentesis are essential in patients with severe hypoxaemia or circulatory shock, although positive end-expiratory pressure ventilation might decrease cardiac output and should therefore be avoided[168,178]. Pericardiocentesis is best performed under echocardiographic guidance (Fig. 4d–f). Echocardiography is used to identify the chest wall location that is closest to the greatest accumulation of pericardial effusion in diastole (Fig. 4e), to identify and mark the site of puncture, and to minimize risk of cardiac perforation and injury to other structures, either in the subxiphoid or apical region (Fig. 4f). The echocardiographic transducer is used to define needle trajectory before needle insertion. After achieving pericardial access, the plastic cannula should be advanced into the pericardial space and the needle withdrawn. Intrapericardial position is subsequently confirmed by injection of agitated saline contrast through the plastic cannula. Linear ultrasonography probes should be used when real-time imaging is needed to visualize intraprocedural needle position. Curvilinear ultrasonography transducers should not be used for this purpose, they are unable to accurately identify the needle tip[179]. Echocardiographic guidance can be combined with fluoroscopy[32,135,180,181]. During the procedure, measures should be taken to prevent secondary bacterial infection of the pericardium.

The most serious complications of pericardiocentesis include laceration and puncture of the myocardium and coronary vessels, perforation of the peritoneal cavity or abdominal viscera, pneumothorax, and vasovagal bradycardia. Very rare complications include internal mammary artery fistulas, acute pulmonary oedema and purulent pericarditis[178]. The risk of serious complications was notably diminished after the introduction of fluoroscopy along with echocardiography and guidance[182,183]. Echocardiography-guided pericardiocentesis was introduced at the Mayo Clinic in 1979 (ref. 184) and is widely used nowadays. The fluoroscopic approach was the first imaging system used for percutaneous pericardiocentesis[32] (Fig. 4a–c). Although major complications are rare, blood for transfusion (400–600 ml) should be available and cross-matched before pericardiocentesis[32,179].

Marked pericardial inflammation can lead to constrictive haemodynamics after pericardiocentesis. This condition is difficult to manage as constriction induces fluid overload that can be worsened by corticosteroids and NSAIDs. In these patients, moderate doses of corticosteroids (for example, 25 mg prednisone) or anakinra could be considered, particularly when fever, neutrophil leukocytosis and pleuropulmonary involvement are also present and the CRP level is elevated[168]. In a case study of effusive–constrictive pericarditis initially manifesting with cardiac tamponade, treatment with anakinra was effective[185]. Furthermore, anakinra was shown to have a role in reversal of incessant or recurrent constrictive pericarditis in 39 patients[186].

Pericardiocentesis in cardiac tamponade resulting from non-surgical pericardial effusions can be performed from either an apical or subxiphoid approach[187]. In the case of postsurgical pericardial effusions localized posterolaterally that spread to the anterolateral part of the left ventricle, the apical approach is more frequently used. Thus, the apical approach is a possible important option for the treatment of postsurgical cardiac tamponade, and it may decrease the need for surgical intervention[187].

Loculated effusions may be removed by echocardiography-guided pericardiocentesis with simultaneous fluoroscopy, which aids the procedure with safety through the halo phenomenon. This phenomenon allows a precise demarcation of the heart shadow, providing a safer approach while performing an echocardiography-guided pericardiocentesis[135].

During the 21-year study period from 1979 to 2000, 1,127 therapeutic echo-guided pericardiocenteses were performed at Mayo Clinic (Rochester, MN, USA), with a procedural success rate of 97% overall. The total complication rate was 4.7% (major, 1.2%; minor, 3.5%)[127]. These rates did not change significantly over the study period. The use of a pericardial catheter for extended drainage increased from 23% to 75% and rates of effusion recurrence and pericardial surgery decreased significantly over the study period[127]. In a Korean study over the 11-year period from 1993 to 2003 at Yonsei Cardiovascular Center, 291 therapeutic echocardiography-guided pericardiocentesis procedures with pericardial catheter drainage were performed in 272 patients, with an overall procedural success rate of 99%, a major complication rate of 0.7% (2 cases of right ventricular free wall perforation that required emergency surgery) and only 1 procedure-related mortality (<30 days)[188].

Pericardiocentesis for cancer and iatrogenic post-surgery complications (as the most common cause of pericardial effusion) had a high success rate and relatively low complication rate in a large cohort of patients in a Singaporean study[189].

In a retrospective observational study of 269 consecutive patients who underwent percutaneous pericardiocentesis between 2006 and 2016 at University Hospitals Leuven in Belgium (prospective follow-up for up to 10 years; ~66% men), most pericardiocentesis procedures were performed without complications: the right heart was 'punctured' in 0.7%, pneumothorax occurred in 2.6%, pneumomediastinum occurred in 0.4%, pneumopericardium occurred in 1.5% and a punctured peritoneal cavity occurred in 0.7%. Among patients undergoing a primary percutaneous pericardial puncture, 8.6% had a second pericardiocentesis, 8.2% had a subxiphoid pericardial window and 0.4% had a subxiphoid approach followed by video-assisted thoracoscopy. A small effusion was present in 1.9% of patients[190].

In a single centre in Bogotá, Colombia, between 2017 and 2018, subxiphoid was the most common pericardiocentesis approach, guided by fluoroscopy (n = 114, 98.2%), The procedure was successful in 98%

of cases, with perforations of the cardiac chambers in two patients, of whom one required emergency cardiac surgery[62].

Surgical management

Urgent surgical treatment for cardiac tamponade is recommended in patients with severe recent chest trauma, rupture of the ventricular free wall after acute myocardial infarction, type A aortic dissection, purulent pericarditis or iatrogenic haemopericardium when the bleeding cannot be controlled percutaneously and surgical repair of the underlying source of the effusion (trauma, aortic dissection) is required[10].

Surgical drainage of the effusion, usually through a subcostal incision (Fig. 4g,h), is required in cases when the heart cannot be reached by a needle or catheter (loculated effusions situated unilaterally (Fig. 4g) or posteriorly, which is more easily approached thoracoscopically)[191], in delayed haemopericardium or effusions after cardiac surgery, in purulent pericardial effusion, or in tuberculous pericarditis. Open surgical drainage procedures usually lead to the creation of a pericardial window (Fig. 4h) as an effective long-term solution and involve excision of a section of the pericardium to allow free drainage of the effusion, either into the mediastinum (subxiphoid) or into the thoracic cavity (transpleural)[192].

Video-assisted thoracic surgery can be considered when a pericardial window is necessary (such as in patients with cancer who have recurrent effusions or in loculated effusions, even in effusions located posteriorly that cannot normally be reached without open thoracotomy[193]). A video-assisted thoracoscopy pericardial window is less traumatic than anterior thoracotomy and provides better visualization than the subxiphoid approach[194].

Open surgery in this setting has several disadvantages. General anaesthesia carries a risk of sudden hypotension in patients with large effusions or cardiac tamponade, and these procedures necessitate a large (6–8 cm) vertical incision in the upper abdomen and, in some cases, resection of the xiphoid process.

Using a nationally representative sample of 44,637 patients, of whom 64.7% underwent pericardiocentesis and the rest surgical drainage for initial management of pericardial effusion or cardiac tamponade[194], pericardiocentesis was associated with greater odds of cardiac complications but lower odds of infection, respiratory failure and blood transfusions compared with surgical drainage[194]. Nevertheless, pericardiocentesis was associated with greater odds of mortality, reintervention and 30-day readmission but similar 30-day cumulative costs compared with surgical drainage. The two strategies yielded similar 30-day cumulative costs[194]. In a nationwide survey-based study in the Netherlands[195], all interventional cardiologists and cardiothoracic surgeons were questioned regarding their preferred diagnostic and treatment modality (pericardiocentesis versus surgical drainage), revealing substantial variation in the preferred management of pericardial effusions among hospitals and clinicians, even within the same centre, possibly due to the lack of specific guidelines[195].

Quality of life

In the modern era of disease management, patients are living longer and quality of life has become increasingly important. Cardiac tamponade is associated with a spectrum of symptoms affecting patient quality of life. The underlying aetiology of the pericardial effusion needs to be investigated, diagnosed and treated to minimize the recurrence of cardiac tamponade after treatment. The majority of patients promptly and completely recover after drainage of pericardial fluid if the cause is treatable. However, in patients with pericardial malignancies or severe perimyocarditis, quality of life and long-term prognosis can be poor[81]. Patients with malignant effusions also commonly experience cachexia and multiple comorbidities that can detrimentally affect their quality of life[196].

Cardiac rehabilitation has been recognized as the most cost-effective intervention to ensure favourable outcomes after cardiac surgery by reducing cardiovascular mortality, morbidity, and disability and improving quality of life[197]. The Functional Evaluation and Cardiac Rehabilitation Working Group of the French Society of Cardiology reported only 1 patient with cardiac tamponade out of 25,420 patients (78% men) of whom 34.3% after coronary bypass and 18.4% after valvular surgery in 65 cardiac rehabilitation canters during a 1-year period. The patient with cardiac tamponade required urgent surgical treatment after experiencing a cardiovascular event during exercise training after aortic valve replacement[198]. Patients undergoing cardiac surgery are older and have complex pathologies and several comorbidities[197,199].

New components of cardiac rehabilitation have been recommended, particularly with regard to the need for appropriate assessment and management of malnutrition and pain[200]. In patients with depression or anxiety, psychotherapy, medication or collaborative care are essential[197]. Frailty is fairly common in elderly patients (10–50%) and is an independent prognostic indicator in this population[173]. Anecdotal evidence suggests that exercise should be avoided in patients with active pericarditis. Complete resolution of the disease can take up to 3 months in severe cases, at which point a return to physical activity should be re-evaluated[201–203].

Outlook

Despite substantial new data and progress towards evidence-based medicine, several issues remain in patients with cardiac tamponade that require further research. First, no worldwide, epidemiological data have been published. Second, most cases of cardiac tamponade from single-centre studies are idiopathic in aetiology, and further diagnostic and therapeutic tools are required to facilitate individualized treatment and to develop guidelines for optimal management of cardiac tamponade. Excellent imaging tools are available to help with the diagnosis, management and treatment of pericarditis and tamponade. Furthermore, recent work implicating the inflammasome has contributed to the use of mechanism-based treatment of common forms of pericarditis. When cardiac tamponade is caused by systemic diseases that involve the heart, improving the management of these diseases is likely the best approach to improve the treatment and prevention of cardiac tamponade.

Several specific open research questions remain unanswered. For example, the appropriate management of patients with large, asymptomatic (or oligosymptomatic) idiopathic pericardial effusions is a matter of debate. Some cardiologists favour prompt pericardiocentesis and diagnosis of the underlying aetiology, whereas other centres opt for a more conservative approach (watch and wait). The conservative approach is adopted because routine analysis of pericardial fluid rarely provides a diagnosis not already presumed by imaging techniques[204,205] and because post-cardiac injury syndromes can occasionally be triggered by invasive procedures such as pericardiocentesis and pericardial window[27]. The superiority of one approach over the other has not yet been demonstrated.

To improve the diagnostic utility of pericardial fluid assessment, research is needed to determine the levels of protein, albumin and lactate dehydrogenase associated with acute pericarditis as compared

with other pericardial conditions. Characterizing the cellular infiltrate in pericardial liquid and tissue to identify the cell types and molecular mechanisms involved in inflammasome activation in pericarditis (for example, the role of IL-1α) is an important area for future investigation. Analysis of cytokines, particularly IL-1 and IL-6, and the transcriptome in pericardial fluid could help elucidate the pathogenesis of idiopathic effusions and identify potential biomarkers that could be validated in future studies. In addition, the biology of pericardial mesothelial cells remains elusive but they are likely to be the source of local IL-1α during active inflammation and may be recognized in future research as a diagnostic or therapeutic target.

The discovery that one-third of patients with pectus excavatum have a concomitant pericardial effusion[31] raises the possibility that other anatomical chest abnormalities have a role in pericardial fluid accumulation. Worldwide registries are needed to assess the incidence, clinical features and outcome of large pericardial effusions and cardiac tamponade. However, securing funding for investigations in patients with these conditions is becoming increasingly difficult.

New medical therapies for severe acute pericarditis are available but should be refined. The NLRP3 inflammasome has been recognized as an important new therapeutic target in myopericardial disorders[206]. Anti-IL-1 agents, such as anakinra and rilonacept, can now be considered for patients with fever, neutrophil leukocytosis, or pleuropulmonary involvement and CRP elevation, in whom corticosteroids are contraindicated[170]. Training of young cardiologists will be a priority as pericardiocentesis is not a trivial procedure and each centre needs to be able to respond quickly and safely with knowledge of the latest research and techniques. Finally, as no specific studies have been published on quality of life after cardiac tamponade as an isolated entity, an urgent need exists for further investigation in this area.

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